

CLINICAL TRIAL PLANNING GRANT

Release Date: October 1, 2001

RFA: RFA-AR-02-001

National Institute of Arthritis and Musculoskeletal and Skin Diseases

(<http://www.nih.gov/niams/>)

Letter of Intent Receipt Date: February 22, 2002

Application Receipt Date: March 22, 2002

THIS RFA USES "MODULAR GRANT" AND "JUST-IN-TIME" CONCEPTS. MODULAR INSTRUCTIONS MUST BE USED FOR RESEARCH GRANT APPLICATIONS REQUESTING LESS THAN \$250,000 PER YEAR IN ALL YEARS. MODULAR BUDGET INSTRUCTIONS ARE PROVIDED IN SECTION C OF THE PHS 398 (REVISION 5/2001) AVAILABLE AT <http://grants.nih.gov/grants/funding/phs398/phs398.html>.

PURPOSE

The purpose of the NIAMS Clinical Trial Planning Grant is to provide support for the organization of activities critical for the successful implementation of clinical trials in areas within the NIAMS mission. The planning grant is intended to (a) allow for early peer review of the rationale and design for high risk, complex, or large-scale clinical trials; (b) provide support for the development of a detailed clinical trial research plan, including a manual of operations and procedures, as a means of decreasing the long start-up time often needed for initiating large trials after award; and (c) provide support to refine critical components of a clinical trial, such as experimental design, analytical techniques, recruitment strategies, data management, and collaborative arrangements. The purpose of the NIAMS planning grant is not to obtain preliminary data nor to conduct studies to support the rationale for the clinical trial.

Applicants should be aware that the award of a planning grant does not guarantee NIAMS acceptance of the full-scale clinical trial for peer review, nor subsequent funding of the trial following peer review. However, it is expected that the applicant will develop a full-scale clinical trial for submission to a public or private agency if the Clinical Trial Planning Grant is approved for funding.

HEALTHY PEOPLE 2010

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This Request for Applications (RFA), Clinical Trial Planning Grant, is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at <http://www.health.gov/healthypeople/>.

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators.

MECHANISM OF SUPPORT

This RFA will use the National Institutes of Health (NIH) R21 award mechanism. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. Applicants can request direct costs in \$25,000 modules, up to a total direct cost request of \$100,000. This is a one-year award. For the purposes of this solicitation the research plan for the application must be limited to 15 pages and appendix material will not be accepted. This RFA is a one-time solicitation. Future unsolicited competing continuation applications will compete with all investigator-initiated applications and be reviewed according to the customary peer review procedures.

FUNDS AVAILABLE

It is estimated that \$600,000 total costs will be available for support of this initiative. Direct costs will be awarded in modules of \$25,000, less any overlap or other necessary administrative adjustments. Facilities and Administrative costs will be awarded based on the negotiated rates. Awards are contingent on the availability of funds and the receipt of highly meritorious applications.

RESEARCH OBJECTIVES

Background

Complex, high risk, or large-scale clinical trials require extensive planning. The NIAMS Clinical Trial Planning Grant supports the development of specific elements essential to the conduct of a successful clinical trial. Examples of these elements include adequate plans for recruitment and retention of patients, experimental design and protocols, data management, analytical techniques, identification of facilities, administrative procedures, and collaborative arrangements. Detailed information regarding the rationale of the clinical trial, based on adequate, preclinical science and preliminary clinical research, must be developed prior to submission and included in the application for a Clinical Trial Planning Grant. The purpose of the planning grant is not to obtain preliminary data or to conduct studies to support the rationale for the clinical trial. The expected product of the Clinical Trial Planning Grant is a detailed clinical trial research plan including a complete manual of operations and procedures (MOP). The NIAMS Clinical Trial Planning Grant is intended to help support this and other related activities necessary for a successful clinical trial.

For some diseases of interest to the NIAMS the design and implementation of successful clinical trials has been hampered by the lack of refined outcome measures, difficulties with recruitment of patients with rare diseases, and lack of information about standardization of procedures among participating clinics. The NIAMS Clinical Trial Planning Grant also provides an opportunity to support these activities.

Examples of Research Objectives for the Planning Period

The actual activities performed during the planning period will depend upon the nature of the trial, and the degree to which the investigators have already developed their trial. The planning activities should be such that they would enable imminent commencement of the actual clinical trial. A few examples are:

- o Testing recruitment strategies
- o Developing subject retention strategies
- o Conducting meetings to address issues such as trial design, methodologies, etc.
- o Preparing a Manual of Operations and Procedures (MOP), a specific safety plan, etc.

Other

Detailed information regarding the rationale of the clinical trial, based on adequate preclinical science and preliminary clinical research, must be developed prior to submission and included in the Clinical Trial Planning Grant application. The purpose of the planning grant is not to support activities of a pilot trial or to conduct studies to support the rationale for the clinical trial. Examples of expected products of the planning grant are a complete Manual of Operations and Procedures, validated outcome measures, or proven feasibility of a new recruitment plan.

Any disease area that is within the NIAMS mission is appropriate for consideration under this RFA.

SPECIAL REQUIREMENTS

The Research Plan should be presented in two parts as described below. Applicants are encouraged to address issues listed in "Review Criteria" and "Specific Review Criteria" in this RFA.

PART 1 - FUTURE CLINICAL TRIAL (Approximately 2-5 pages)

This part may or may not be written using the standard headings of PHS form 398 (Specific Aims, Background and Significance, Preliminary Studies, Research Design and Methods, and Human Subjects) but should clearly describe the following items:

- o Specific Aims, including a clear statement of any hypotheses that the clinical trial would address.
- o Background/Rationale - Provide rationale for the trial. The rationale must be supported by existing data/information. The planning grant is not to be used to conduct studies in order to rationalize the clinical trial.
- o Significance - Give information documenting significance and the need to perform the clinical trial. Describe the potential impact of the clinical trial on health care: What is the need for new therapy? What are the potential advantages and disadvantages of competitive therapies?
- o Research Design and Methods - No details are required, but enough information should be provided to evaluate how the trial would be conducted. Pertinent information must be included

on: (a) Intervention(s) to be used, reasons for the selection of intervention(s), and mode(s) of delivery; (b) study design, treatment group(s), trial size, and inclusion/exclusion criteria (if not developed yet, please state so, and you may include it as a part of your planning grant part 2); (c) control group(s) if applicable; (d) outcome measures; and (e) data analysis plan if applicable.

o Proposed Clinical Sites and Investigators-provide a list. Letters of commitment are not required at this stage.

o Gender, Minorities & Children Issues - Proposed population description in terms of gender, minorities and children; justification for excluding any gender, minority groups or children; plans for recruitment outreach, as appropriate.

o Human Subjects Issues - Ethical considerations for placebo/control groups, risk/benefit for the participants; availability of the requisite eligible patient pool.

PART 2 - PLANNING GRANT (Approximately 10-13 pages)

This part must be written using the PHS form 398 headings, and should include:

a. Specific Aims for the planning period (examples include: "We will prepare a Manual of Operations and Procedures"; "We will conduct meetings to address the following issues."; "We will test recruitment strategies"; "We will organize essential safety committees"; etc.).

b. Background and Significance, including rationale for planning period; Why is the planning period needed? Why not start the trial now?

c. Preliminary Studies - Not required, but if any preliminary work already completed is included, it should be relevant to the work proposed in the planning period, and to the trial proposed in Part 1.

d. Research Design and Methods - Detailed approach for each Specific Aim of the planning period. Highlight any innovations applicable to the planning period.

e. Human Subjects - Address all the required items on human subjects for anticipated issues arising in the planning phase. If no human subjects issues are involved during the planning period, state so.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification are provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing research involving human subjects should read the UPDATED "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research," published in the NIH Guide for Grants and Contracts on August 2, 2000

(<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-048.html>); a complete copy of the updated Guidelines is available at

http://grants.nih.gov/grants/funding/women_min/guidelines_update.htm:

The revisions relate to NIH defined Phase III clinical trials and require: a) all applications or proposals and/or protocols to provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) all investigators to report accrual, and to conduct and report analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research conducted or supported by the NIH unless there are scientific or ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the Inclusion of Children as Participants in Research Involving Human Subjects that was published in the NIH Guide for Grants and Contracts, March 6, 1998, and is available at the following URL address: <http://grants.nih.gov/grants/guide/notice-files/not98-024.html>.

Investigators also may obtain copies of these policies from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning a particular policy.

URLS IN NIH GRANT APPLICATIONS OR APPENDICES

All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Reviewers are cautioned that their anonymity may be compromised when they directly access an Internet site.

REQUIRED EDUCATION ON THE PROTECTION OF HUMAN SUBJECT PARTICIPANTS

NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for research involving human subjects. This policy announcement is found in the NIH Guide for Grants and Contracts Announcement dated June 5, 2000, at the following website: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html>.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT

The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at: http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm

Applicants may wish to place data collected under this RFA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

LETTER OF INTENT

Prospective applicants are asked to submit, by February 22, 2002, a letter of intent that includes a descriptive title of the proposed research, the name, address, and telephone number of the

Principal Investigator, the identities of other key personnel and participating institutions, and the number and title of this RFA in response to which the application would be submitted.

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows NIAMS staff to estimate the potential review workload and plan the review. The letter of intent is to be sent to Tommy L. Broadwater, Ph.D. at the address listed under INQUIRIES by February 22, 2002.

APPLICATION PROCEDURES

The PHS 398 research grant application instructions and forms (rev. 5/2001) at <http://grants.nih.gov/grants/funding/phs398/phs398.html> must be used in applying for these grants. This version of the PHS 398 is available in an interactive, searchable PDF format. For further assistance contact GrantsInfo, Telephone 301/435-0714, Email: GrantsInfo@nih.gov.

SPECIFIC INSTRUCTIONS FOR MODULAR GRANT APPLICATIONS

The modular grant concept establishes specific modules in which direct costs may be requested as well as a maximum level for requested budgets. Only limited budgetary information is required under this approach. The just-in-time concept allows applicants to submit certain information only when there is a possibility for an award. It is anticipated that these changes will reduce the administrative burden for the applicants, reviewers and NIH staff. The research grant application form PHS 398 (rev. 5/2001) at <http://grants.nih.gov/grants/funding/phs398/phs398.html> is to be used in applying for these grants, with modular budget instructions provided in Section C of the application instructions. Applicants are permitted, however, to use the 4/1998 revision of the PHS 398 for scheduled application receipt dates until January 9, 2002. If you are preparing an application using the 4/1998 version, please refer to the step-by-step instructions for Modular Grants available at <http://grants.nih.gov/grants/funding/modular/modular.htm>. Additional information about Modular Grants is also available on this site.

The RFA label available in the PHS 398 (rev. 5/2001) application form must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked. The RFA label is also available at: <http://grants.nih.gov/grants/funding/phs398/label-bk.pdf>.

Submit a signed, typewritten original of the application, including the Checklist, and three signed, photocopies, in one package to:

CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040, MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for express/courier service)

At the time of submission, three additional copies of the application must be sent to:

Dr. Tommy L. Broadwater
Extramural Program
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Building 45, Room 5AS.25U
Bethesda, MD 20892-6500
Telephone: (301) 594-4952
FAX: (301)-402-2406
Email: broadwat@mail.nih.gov

Applications must be received by the application receipt date listed in the heading of this RFA. If an application is received after that date, it will be returned to the applicant without review.

The Center for Scientific Review (CSR) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. The CSR will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of substantial revisions of applications already reviewed, but such applications must include an Introduction that addresses the previous critique.

REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness by CSR and responsiveness by NIAMS staff. Incomplete and/or non-responsive applications will be returned to the applicant without further consideration.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the NIAMS in accordance with the review criteria stated below. As part of the initial merit review, all applications will receive a written critique. Applications may undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, are discussed, assigned a priority score, and receive a second level review by the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council.

REVIEW CRITERIA

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments reviewers will be asked to discuss the following aspects of the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in assigning the overall score, weighting them as appropriate for each application. Note that the application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

Please note that there may be high enthusiasm for the future trial (part 1) but little enthusiasm for the planning (part 2), or vice versa, or high enthusiasm for both, etc. Review committees should indicate their enthusiasm for the two sections separately (with only one priority score for the overall application).

SPECIFIC REVIEW CRITERIA

The criteria used to evaluate Clinical Trial Planning Grant applications are based on the "Specific Requirements," as spelled out in an earlier section of the RFA. The reviewers will provide a two-part critique on the application.

- o PART 1 - This will be a brief critique of the future clinical trial, and will be based upon the items requested under part 1 of "Special Requirements" of this RFA. General enthusiasm (low, medium, high) about the proposed trial should be based on the following:

(1) Significance: Would the future clinical trial address an important problem? Would conduct of the trial influence standard of care, develop a new therapy, or provide a better understanding of the disease? Is there convincing rationale to conduct the trial?

(2) Investigator: Is the investigative team qualified to conduct the clinical trial?

(3) Feasibility: Do the research design and methods appear appropriate and reasonable for the successful conduct of the proposed trial? (Please note that detailed research design and methods are NOT required.)

(4) Human Subjects: Only major ethical concerns surrounding human subjects should be noted.

o PART 2 - This will be a detailed critique of the planning period activities, and will be based upon the items requested under part 2 of "Special Requirements" of this RFA.

(1) Significance: Will the proposed planning process address major barriers in conducting the future clinical trial? Is the planning period necessary?

(2) Approach: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

(3) Innovation: Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

(4) Investigator: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

(5) Environment: Does the environment in which the work will be done contribute to the probability of success? Do the proposed Aims take advantage of unique features of the environment or employ useful collaborative arrangements? Is there evidence of institutional support?

(6) Gender, Minorities, and Children: (Applicable only if human subject issues are involved in the planning period.) The adequacy of plans to include both genders, minorities, and children as appropriate for the scientific goals of the research will be evaluated.

(7) Human Subjects: (Applicable only if human subject issues are involved in the planning period) Ethical issues surrounding human subjects will also be evaluated.

SCHEDULE

Letter of Intent Receipt Date: February 22, 2002

Application Receipt Date: March 22, 2002

Peer Review Date: TBA

Council Review: September 26, 2002

Earliest Anticipated Start Date: September 30, 2002

AWARD CRITERIA

Award criteria that will be used to make award decisions include:

- o scientific merit (as determined by peer review)
- o availability of funds
- o programmatic priorities.

INQUIRIES

Inquiries concerning this RFA are encouraged. The opportunity to clarify any issues or answer questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to one of the following persons, according to scientific area:

Dr. Joan McGowan

Bone Diseases

45 Center Drive, Room 5AS-43E

Bethesda, MD 20892-6500

Telephone: (301) 594-5055

FAX: (301) 480-4543

Email: mcgowanj@mail.nih.gov

Dr. Alan N. Moshell

Skin Diseases

45 Center Drive, Room 5AS-25L

Bethesda, MD 20892-6500

Telephone: (301) 594-5017

FAX: (301) 480-4543

Email: moshella@mail.nih.gov

Dr. James S. Panagis

Orthopaedics

45 Center Drive, Room 5AS-37K

Bethesda, MD 20892-6500

Telephone: (301) 594-5055

FAX: (301) 594-4543

Email: panagisj@mail.nih.gov

Dr. Susana A. Serrate-Sztein

Rheumatic Diseases

45 Center Drive, Room 5AS-37G

Bethesda, MD 20892-6500

Telephone: (301) 594-5032

FAX: (301) 480-4543

Email: szteins@mail.nih.gov

Direct inquiries regarding review issues to:

Tommy L. Broadwater, Ph.D.

Scientific Review Branch

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Natcher Building, Room 5AS-25U

45 Center Drive, MSC 6500

Bethesda, MD 20892-6500

Telephone: (301) 594-4952

FAX: (301) 480-4543

Email: broadwat@mail.nih.gov

Direct inquiries regarding fiscal matters to:

Melinda Nelson

Grants Management Office

National Institute of Arthritis and Musculoskeletal and Skin Diseases

45 Center Drive, Room 5AS-49F, MSC 6500

Bethesda, MD 20892-6500

Telephone: (301) 594-3535

FAX: (301) 480-5450

Email: nelsonm@mail.nih.gov

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.846. Awards are made under authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and administered under NIH grants policies and Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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